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Synthesis of Chromeno[2,3-*d*]imidazol-9(1*H*)-ones via Tandem Reactions of 3-Iodochromones with Amidines Involving Copper-Catalyzed C−H Functionalization and C−O Bond Formation

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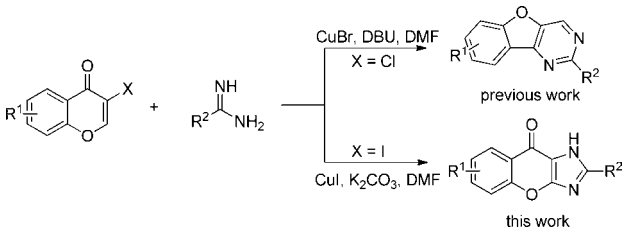
ABSTRACT



A novel six-membered heterocyclic skeleton of imidazochromone was prepared via an efficient one-pot reaction including a key step of copper-catalyzed aerobic C−H intramolecular cycloetherification. Notably, this process does not require the presence of strong para electron-withdrawing groups on the phenol component. Also, the results of this effort show that acyl phenols containing electron-rich heterocycles participate in an efficient C−H activation/C−O formation process.

Structurally complex and functionally diverse heterocycles play important roles as lead compounds in efforts aimed at the discovery of new pharmaceutical agents. Among the various synthetic approaches to these substances, those that utilize tandem reactions of readily accessible starting materials are highly attractive, owing to their simplicity and atom economy.[1] In this regard, the processes involving transition-metal-catalyzed, directing C−H activation/C−heteroatom bond formation have been extensively explored.[2] In comparison to other late transition metals employed for these reactions, copper is a particularly attractive catalyst because of its low cost and toxicity.[3] Indeed, copper-catalyzed reactions that occur via directing group guided intramolecular C−H amination have been developed for the synthesis of five- and six-membered nitrogen-containing heterocyclic compounds.[4]

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(3) For selected Cu-catalyzed C−H activation reviews, see: (a) Campbell, A. N.; Stahl, S. S. *Acc. Chem. Res.* **2012**, *45*, 851–863. (b) Wendlandt, A. E.; Suess, A. M.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 11062–11087. (c) Zhang, M. *Appl. Organomet. Chem.* **2010**, *24*, 269–284.

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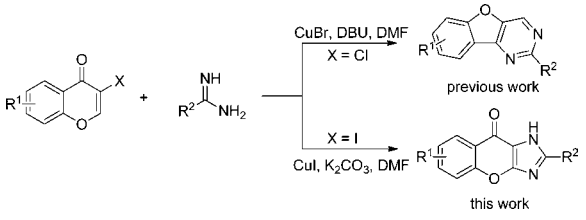
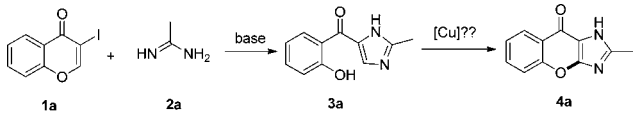
In addition, new processes devised for the preparation of five-membered oxygen-containing heterocycles take advantage of amide carbonyl oxygen, which directs intramolecular C−H etherification promoted by a copper salt along with oxygen as the terminal oxidant.[5] Nevertheless, the use of phenols as oxygen donors in copper-catalyzed C−H etherification processes is rare, due to the instability of these substances at high temperature in the presence of strong oxidants[6] and competitive phenol homocoupling reactions.[7] In 2012, Zhu et al. demonstrated that Cu-catalyzed oxidative annulation of *o*-arylphenols could facilitate this process to form dibenzofuran when an electron-withdrawing group was present at the para position of the phenol moiety.[8] Inspired by the success of the investigations described above and the results of our recent studies focusing on methods for the synthesis of highly reactive substituted chromones,[9] we designed a new approach to the preparation of chromeno[2,3-*d*]imidazol-9(1*H*)-ones from 3-iodochromones, which involved a copper-catalyzed C−H functionalization and C−O bond formation reaction (Scheme 1).

Scheme 1. Reactions of Substituted 3-Halogenated Chromones



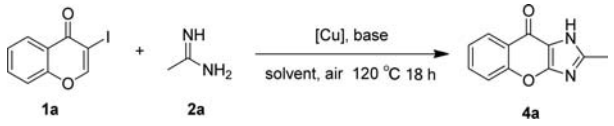
In an earlier study, we observed that 3-chlorochromones reacted with amidines in a copper(I)-promoted process under basic conditions, which proceeded via a tandem pathway involving a chemoselective Michael addition−elimination−double intramolecular cyclization sequence (Scheme 1).[9a] In contrast, we observed that 3-iodochromone, containing the superior iodine leaving group, reacted with acetamidine hydrochloride under basic conditions to form the (imidazolyl)(phenyl) methanone **3a**. A consideration of both processes suggested the potential of a new approach for the preparation of a previously unknown class of six-membered heterocycles possessing the structure of chromeno[2,3-*d*]imidazol-9(1*H*)-one **4a**.[10] Specifically, we postulated that(imidazolyl)(phenyl)methanones **3a** would be converted to chromeno[2,3-*d*]imidazol-9(1*H*)-ones **4a** (Scheme 2) through a tandem, copper-catalyzed C−H functionalization and C−O bond formation process.

Scheme 2. Copper-Catalyzed C−H Activation/C−O Formation



In order to determine if the proposed one-pot process happened, reactions of 3-iodochromone **1a** with acetamidine hydrochloride **2a** were carried out by using different bases, solvents, and copper catalysts. To our delight, we smoothly obtained the new title class of six-membered ring with an imidazochromone framework which had not been reported in early literature. The result (Table1) showed that the use of DBU in DMF and a catalytic amount of copper iodide promoted a very inefficient C−H functionalization/C−O formation process (Table 1, entry 1). However, when inorganic bases were employed for this convertion, **4a** was

Table 1. Optimization of Reaction Conditions[a]



entry	cat.	base	solvent	yield (%)[b]
1	CuI	DBU	DMF	trace
2	CuI	K_2CO_3	DMF	82
3	CuI	Cs_2CO_3	DMF	70
4	CuI	KOAc	DMF	65
5	CuI	CsOPiv	DMF	77
6	CuI	K_2CO_3	DMSO	33
7[c]	CuI	K_2CO_3	DMF	20
8[d]	CuI	K_2CO_3	DMF	86
9	CuCl	K_2CO_3	DMF	30
10	CuBr	K_2CO_3	DMF	33
11	$CuCl_2$	K_2CO_3	DMF	41
12	$CuBr_2$	K_2CO_3	DMF	52
13	$CuSO_4$	K_2CO_3	DMF	38
14	$Cu(OAc)_2$	K_2CO_3	DMF	45
15	$Cu(OTf)_2$	K_2CO_3	DMF	80
16[e]		K_2CO_3	DMF	0
17[f]	CuI	K_2CO_3	DMF	trace
18[g]	CuI	K_2CO_3	DMF	80
19[h]		K_2CO_3	DMF	0

[a] General conditions: mixture of **1a** (0.4 mmol), **2a** (0.4 mmol), base (1.2 mmol), and copper salts (10 mol %) in solvent (3 mL). [b] Isolated yield. [c] Reaction was carried out under an Ar atmosphere. [d] 20 mol % CuI was used. [e] Only **3a** remained. [f] 1.0 equiv of K_2CO_3 was used. [g] 1.2 equiv of TEMPO (radical scavenger) was added into the reaction system. [h] 1.2 equiv of TEMPO was added without copper; only **3a** remained.

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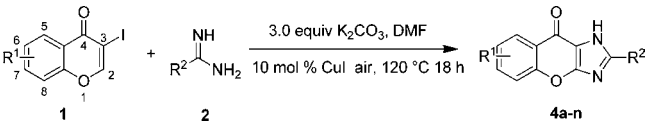
generated in 65−82% yields (Table 1, entries 2−5). The results led to the identification of K_2CO_3 as the optimal base and showed that DMSO was not an ideal solvent. Moreover, the reaction that was performed under an Ar atmosphere resulted in the formation of **4a** in a low (20%) yield along with remaining acyl phenol **3a** (Table 1, entry 7). This was an expected result, because oxygen was generally the primary oxidant in copper-catalyzed oxidative C−H functionalization reactions. Further studies showed that increasing the amount of CuI (0.2 equiv) caused a comparably higher product yield (Table 1, entry 8). The results of screening of other copper sources, including $Cu(OTf)_2$, demonstrated that both copper(I) and copper(II) salts could accelerate this process in variable yields (Table 1, entries 9−15). In addition, it was noteworthy that the cyclization from **3a** to **4a** would not take place in the absence of either base or copper salts (Table 1, entries 16 and 17). In addition, a radical scavenger barely had an effect on the whole reaction (Table 1, entry 18) and TEMPO was added without CuI to give **3a** only (Table 1, entry 19). Certainly we also divided the reaction into two parts, in which the copper catalyst was added into the bottle after former process was finished. This gave a satisfying result as well, which also proved the occurrence of a copper-catalyzed direct C−O coupling process during the transformation of **3a** into **4a**.

Consequently, the scope of substrates for this one-pot tandem reaction was explored under the optimized conditions. The results (Table 2) showed that the electronic nature of substituents on the chromone ring had a pronounced effect on the efficiency of the copper-catalyzed annulation reaction. For example, the 3-iodochromone containing a OMe group at C-7 underwent a more efficient reaction process (Table 2, entry 4). In contrast, the presence of an electron-donating OMe group at C-6 of the chromone ring system delivered the corresponding product in diminished yield for uncertain reasons; perhaps it weakened the stability of the intermediate during the cyclization process or it was liable to be oxidated to quinones (Table 2, entry 3).[11] In addition, the presence of a mild electron-withdrawing fluoro substituent at either C-6 or C-7 of the chromone ring system had an obvious impact on the efficiency of this reaction. The results of the exploration probing the effect of changing the amidine reactant showed that both sterically encumbered alkyl and mild electron-withdrawing substituents on the amidine carbon did not greatly impact the yield of the reaction. However, when the amidine contained strong electron-withdrawing groups such as *p*-nitrophenyl and 4-pyridyl, the efficiency of the process was greatly influenced and the reaction product was complex with a mixture of side products and a large amount of noncyclized products **3n** and **3o**, respectively (Table 2, entries 14 and 15). As an aside, the structure of **4h** was unambiguously determined by using X-ray crystallographic analysis (Figure 1).[12]

Table 2. Scope of the Cascade Reaction of **1** with **2**[a]



1 **2** **4a-n**

Entry	R^1	R^2	Product	Yield(%)[b]
1	H	Me	**4a**	82
2	6-F	Me	**4b**	57
3	6-OMe	Me	**4c**	40
4	7-OMe	Me	**4d**	83
5	7-F	Me	**4e**	42
6	7-Me	Me	**4f**	65
7	H	Ph	**4g**	70
8	H	*t*-Bu	**4h**	88
9	H	H	**4i**	73
10	H		**4j**	63
11	H		**4k**	60
12	H		**4l**	58
13	H		**4m**	70
14[c,d]	H		**4n**	45
15[d]	H		**4o**	trace

[a] Unless noted, the reactions were conducted under the optimized conditions. [b] Yields of isolated compounds. [c] reaction time required 36 h. [d] large amount of noncyclized product remained.

A further investigation probing the synthetic utility of the copper-catalyzed C−H functionalization and C−O bond formation was carried out by using intermediate acyl phenols derived from other five-membered heterocycles (Scheme 3).[13] The observations made in this effort demonstrated that the more electron-rich pyrrole **5a**[14] underwent cyclization efficiently to give **6a** in 68% yield. However, the

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(12) CCDC 928999 (**4h**) contains supplementary crystallographicdata for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data-request/cif.

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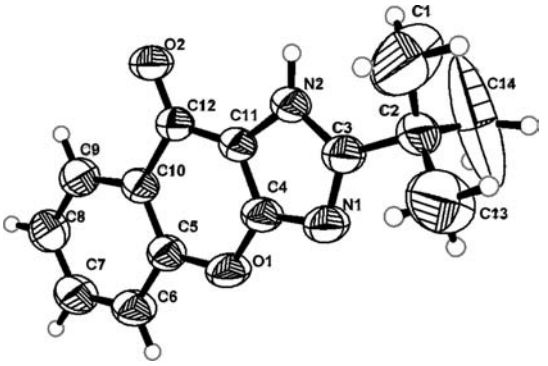
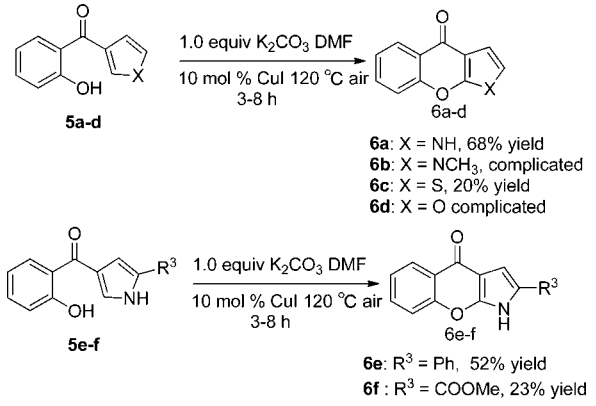


Figure 1. X-ray structure of **4h**.

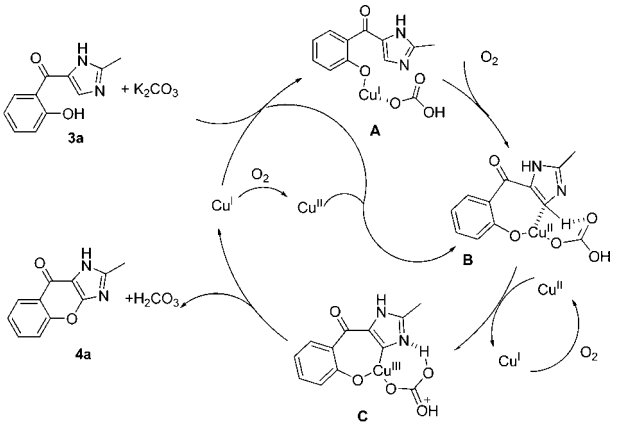
N-methylpyrrole analogue **5b** reacted under identical conditions to form a complicated mixture. In addition, the pyrrole substrate **5e** containing a phenyl group at C-2 underwent efficient cyclization, while the 2-methoxycarbonyl species **5f** bearing an electron-withdrawing group reacted to form **6f** in an attenuated yield (23%). Finally, the reactant **5c** containing a thiophene ring and the relatively more electron deficient furan **5d** both went through a highly inefficient process to give rise to complicated product mixtures.

Scheme 3. C−H Activation/C−O Bond Formation of Other Heterocycle-Substituted Acyl Phenols



On the basis of the preliminary results described above, including the fact that the whole reaction is not susceptible in the presence of TEMPO, which rules out the probability of a radical mechanism such as SET,[3b] and oxidant without copper reagent also has no impact on the reaction, which excludes an addition/oxidation mechanism. We hypothesize a copper catalytic cycle of this transformation (Scheme 4). In the cycle, the phenolic hydroxy group of intermediate **3a**, formed by the reaction of **1a** with **2a** under

Scheme 4. Possible Pathway for Copper-Catalyzed C−H Cycloetherification



basic conditions, combines with Cu(I) catalyst to form complex **A**. Rapid oxidation of **A** then generates the more electrophilic Cu(II) complex precursor, which is prone to undergo an agostic C−H interaction[15] owing to the electron-rich nature of the heterocycle and following carbonate-assisted formation of a six-membered cyclic transition state gives the Cu(II) complex **B**. Also, it is possible that Cu(II) complex **B** can be directly generated by the reaction of Cu(II) species with **3a**. Finally, disproportionation of the Cu(II) complex **B**[16] produces aryl- Cu(III) complex **C**, which affords the final cyclization product **4a** and recyclable Cu(I) via direct reductive elimination.

In summary, we have developed a simple and efficient one-pot copper-catalyzed direct C−O coupling method to form a novel imidazochromone scaffold. Only a catalytic amount of CuI and 3.0 equiv of K_2CO_3 were employed to promote the whole reaction efficiently. To broaden the application of Cu-catalyzed aerobic C−H activation, we attempted to use other heterocycles as the substrates of the cyclization reaction and found that electron-rich heterocycles can facilitate the cycloetherification remarkably.

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Supporting Information Available. Text and figures giving 3xperimental procedures and full spectroscopic data for all new compounds above. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.